

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 July 2001 (09.07.01)	Applicant's or agent's file reference 4-31153A
International application No. PCT/EP00/09346	
International filing date (day/month/year) 25 September 2000 (25.09.00)	
Priority date (day/month/year) 27 September 1999 (27.09.99)	
Applicant ACEMOGLU, Murat et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

17 April 2001 (17.04.01)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Claudio Borton
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REC'D 10 APR 2002

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

8

Applicant's or agent's file reference 4-31153A	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/09346	International filing date (day/month/year) 25/09/2000	Priority date (day/month/year) 27/09/1999
International Patent Classification (IPC) or national classification and IPC C07C229/00		
Applicant NOVARTIS AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17/04/2001	Date of completion of this report 08.04.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Pauwels, G Telephone No. +31 70 340 2379 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09346

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*):

Description, pages:

1-45 as originally filed

Claims, No.:

1-6,7 (part) as originally filed

7 (part) as received on 05/02/2002 with letter of 01/02/2002

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09346

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
☐ paid additional fees.
☒ paid additional fees under protest.
☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09346

No: Claims

2. Citations and explanations
see separate sheet

Reference is made to the following documents:

D1: WO-A-9911605

D2: J. Am. Chem. Soc. (1992), 114(13), 5054-67

D3: ANGEWANDTE CHEMIE. INTERNATIONAL EDITION., vol. 37, 1998,
pages 2046-2067,

D4: The Merck Index 12th Edition' 1996 , page ONR-85; paragraph 353

Re Item IV

- 1 The present application concerns processes for the production of 2-phenylamino-5-alkylphenyl acetic acids represented by formula I of claim 1 via a 1-phenyl- 5-alkyl indol-2-one, represented by formula II of claim 1.

For the purposes of unity, a single general inventive concept is required. This means that the broadest possible problem to be solved has to be drawn up (i.e. to cover all claimed possibilities). Thus, by definition, the provisos may not be taken into account when determining the presence or lack of unity, since the special technical feature must define a contribution over these provisos as well.

Several different synthetic pathways leading to the intermediate compound II are disclosed. Some of them use a 4-alkyl diphenylamine, represented by formula VIII of claim 3, as a further precursor. In another set of pathways a 1-phenyl-5-alkyl- 1,4,5,6-tetrahydro indol-2-one is involved.

The document D2, discloses a compound of formula VIII (see page 5056: formula 17; page 5067, right hand column, first paragraph). The document D1 discloses (see example 38 and claim 9(c)): a process for the preparation of a compound of Formula I by cleaving a lactam of Formula II, wherein in both formulae R represents ethyl, R₁, R₂, R₄ and R₅ all represent fluoro and R₃ is hydrogen. The subject-matter of claim 1 therefore differs from this known process in that: the known process is excluded by means of a disclaimer.

The problem to be solved by the present application has been regarded as to provide further processes for the preparation of 2-phenylamino-5-alkylphenyl

acetic acids represented by formula I of claim 1.

With respect to unity of intermediates and final products the "Administrative Instructions under the PCT" Annex B, Part 1, g) v) stipulate that "The intermediate and final products shall not be separated, in the process leading from one to the other, by an intermediate which is not new."

Since intermediate VIII is known and a known intermediate of formula II has been excluded by means of a disclaimer, the requirement of the Administrative Instructions under the PCT, mentioned here above is not met. Since there are no apparent other features which may be regarded as a special technical feature, which could link the different inventions of the application, the present application lacks of unity of invention contrary to Rule 13.1 PCT.

Additionally, the "Administrative Instructions under the PCT" Annex B, Part 1, g) ii) B) require that "the intermediate and final products are technically interrelated, this meaning that the final product is manufactured directly from the intermediate or is separated from it by a small number of intermediates all containing the same essential structural element."

Compounds IX, X and XIII undoubtedly comprise some structural elements of the end product II such as the group R in position 4 of a N-atom and the groups R₁ - R₅ on a phenyl. The further intermediates which lead to the end product all contain these structural elements. Nevertheless compounds IX and XIII are structurally considerably different from II and all three are separated from II by at least three further intermediates: compounds VIII, VII and II.

In the opinion of the ISA, three further intermediates is not a small number in the sense of the Administrative Instructions under the PCT Annex B, Part 1, g) ii) B).

Consequently compounds IX, X and XIII are not technically sufficient closely linked to the end product as to form a single general inventive concept.

- 2 Claim 2 consists of a large number of independent sub-claims with no clear explicit technical relation among them. They all appear to concern intermediate

steps in the preparation of known final compounds. These known final compounds seem to be the only technical feature, which links the subclaims. Because the final compounds are known the subject matters of the sub-claims of claim 2 lack a special technical feature which makes a contribution over the prior art. Hence the group of inventions of claim 2 are not so linked as to form a single inventive concept contrary to Rule 13.1 PCT.

3 The separate groups of invention are:

- 3.1 Process for the production of a compound of formula I from compound II (claim 1); processes for the production of compounds of formula III, VII and VIII (claim 2 a, b, c, d; claim 7 a, b, c, d). Claims: 1-7 all partially.
- 3.2 Process for the production of a compound of formula VIII by reaction of a compound XI with p-toluidine or 4-ethyl-aniline; or by reaction of a compound IV with 4-bromotoluene or 4-bromoethyl benzene (claim 2 f, g). Claims: 1-7 all partially.
- 3.3 Process for the production of a compound of formula VIII from or via compounds IX, X or XII (claim 2 e, h, i, j, k; claim 7 e, f). Claims: 1-7 all partially.
- 3.4 Process for the production of a compound of formula VIII from or via compound XIII (claim 2 l, m, n; claim 7 g). Claims: 1-7 all partially.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Novelty

- 1.1 Claim 1: The process of example 38 of D1 has been disclaimed. The documents D2 to D4 don't concern a process for the production of a compound of Formula I of claim 1.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09346

- 1.2 Claim 2: The processes b), d), f) are different from the processes disclosed on pages 34 and 35 of document D1 because of the disclaimer in claim 1. The documents D1, D2, D3 or D4 don't disclose processes for the preparation of compounds of formula II, III, VII, VIII, IX, X or XIII.
- 1.3 Claim 3: The process is different from the process disclosed on pages 34 and 35 of document D1 because of the disclaimer in claim 1.
- 1.4 Claims 4, 5, 6, 7: The compounds are different from the compound disclosed in D1 because of the substituents R, R¹, R², R³, R⁴ and R⁵.
- 1.5 The subject matter of claims 1-7 is new (Art. 33(2) PCT).

2 Inventive step

- 2.1 The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (see example 38 and claim 9(c)): a process for the preparation of a compound of Formula I by cleaving a lactam of Formula II, wherein in both formulae R represents ethyl, R₁, R₂, R₄ and R₅ all represent fluoro and R₃ is hydrogen. The subject-matter of claim 1 therefore differs from this known process in that: the known process is excluded by means of a disclaimer.
- 2.2 The problem to be solved by the present invention may therefore be regarded as to provide an alternative process for the preparation of a compound of Formula I by cleaving a lactam of Formula II. The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

A disclaimer is, by way of exception, allowable to restore the novelty of a otherwise inventive claim, it cannot impart inventive step to a teaching which is obvious.

- 2.3 Dependent claims 4 and 5 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being as follows: The subject-matter of claims 4 and 5 consists in the selection of the compounds described in document D1. Such a selection can only be regarded as inventive, if the compounds

present unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 4 and 5.

- 2.4 The apparently mutually unrelated processes of the independent claim 2 are usual processes known for the preparation of analogous compounds. For example: the process of claim 2(e) is generally known from document D4; the process of claim 2(f) and 2(g) is generally known from document D3 (see page 2051, last paragraph - page 2051, first paragraph). An inventive step could only be recognized for each of the subclaims if they would be integrated in a new and inventive overall process.

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International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

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(10) International Publication Number
WO 01/23346 A3

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227/22, C07D 209/34, C07C 233/15, 235/24, 235/16,
211/56, 211/52

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(21) International Application Number: PCT/EP00/09346

(22) International Filing Date:
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(74) Agent: **BECKER, Konrad**; Novartis AG, Corporate
Intellectual Property, Patent & Trademark Department,
CH-4002 Basel (CH).

(25) Filing Language: English

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DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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Published:

— with international search report

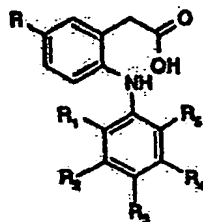
(72) Inventors; and

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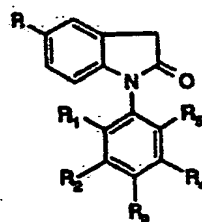
(88) Date of publication of the international search report:
10 January 2002

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PHENYLACETIC ACID DERIVATIVES



(I)



(II)

(57) Abstract: A process for the production of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof, comprising cleaving a lactam of formula (II) wherein the symbols are as defined, with a base; and precursors therefor and processes for the preparation of the precursors. The compounds of formula (I) are pharmaceutically active compounds which are selective inhibitors of Cyclooxygenase (II).

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INTERNATIONAL SEARCH REPORT

Inte Application No

PCT/EP 00/09346

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07C229/42	C07C227/22	C07D209/34	C07C233/15	C07C235/24
	C07C235/16	C07C211/56	C07C211/52		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 11605 A (NOVARTIS AG, SWITZ.;NOVARTIS-ERFINDUNGEN VERWALTUNGS-GESELLSCHAFT M.B.) 11 March 1999 (1999-03-11) claims 1,9	1-7
X	POE, RUSSELL ET AL: "Chemistry and kinetics of singlet pentafluorophenyl nitrene" J. AM. CHEM. SOC. (1992), 114(13), 5054-67, XP002161266 page 5056; figure 17 page 5067, right-hand column, paragraph 1	2,7

-/-

X Further documents are listed in the continuation of box C.

Y Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T"** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y"** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "E"** document member of the same patent family

Date of the actual completion of the international search

15 August 2001

Date of mailing of the international search report

03.09.01

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Authorized officer

Pauwels, G

INTERNATIONAL SEARCH REPORT

Int. Application No.
PCT/EP 00/09346

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J.F. HARTWIG: "Transition metal catalyzed synthesis of arylamines and aryl ethers from aryl halides and triflates: scope and mechanism" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION., vol. 37, 1998, pages 2046-2067, XP002174970 VERLAG CHEMIE. WEINHEIM., DE ISSN: 0570-0833 page 2051, last paragraph -page 2051, paragraph 1	1-5
A	"The Merck Index 12th Edition" 1996, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION NJ XP002174971 page ONR-85, paragraph 353	1-5

INTERNATIONAL SEARCH REPORT

International application N°
PCT/EP 00/09346

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7 all partially

Process for the production of a compound of formula I from compound II (claim 1); processes for the production of compounds of formula III, VII and VIII (claim 2 a, b, c, d; claim 7 a, b, c, d)

2. Claims: 1-7 all partially

Process for the production of a compound of formula VIII by reaction of a compound XI with p-toluidine or 4-ethyl-aniline; or by reaction of a compound IV with 4-bromotoluene or 4-bromoethyl benzene (claim 2 f, g)

3. Claims: 1-7 all partially

Process for the production of a compound of formula VIII from or via compounds IX, X or XII (claim 2 e, h, i, j, k; claim 7 e, f)

4. Claims: 1-7 all partially

Process for the production of a compound of formula VIII from or via compound XIII (claim 2 l, m, n; claim 7 g)

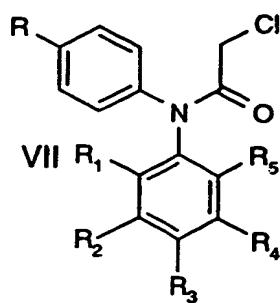
INTERNATIONAL SEARCH REPORT

Information on patent family members

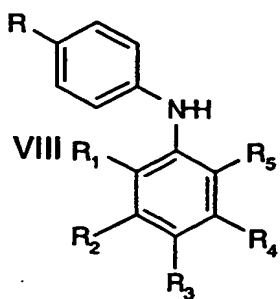
Inte application No

PCT/EP 00/09346

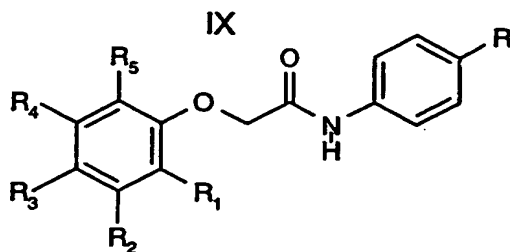
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9911605 A	11-03-1999	AU 9534098 A	22-03-1999
		BR 9812010 A	12-12-2000
		CN 1268112 T	27-09-2000
		EP 1007505 A	14-06-2000
		NO 20000943 A	25-02-2000
		PL 338357 A	23-10-2000
		SK 2472000 A	12-09-2000
		TR 200000447 T	21-07-2000
		ZA 9807785 A	01-03-1999
		HU 0002514 A	28-12-2000



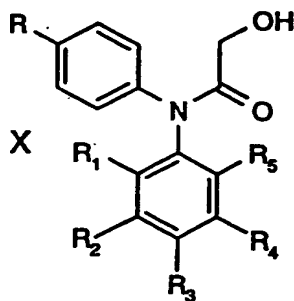
d) a compound of formula VIII



e) a compound of formula IX

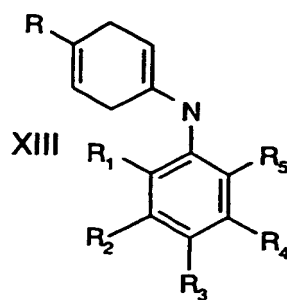


f) a compound of formula X



or

g) a compound of formula XIII



wherein the symbols are as defined in claim 1.